Neuropilins are positive regulators of Hedgehog signal transduction.

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Public Summary:
The Hedgehog (Hh) pathway is essential for vertebrate embryogenesis, and excessive Hh target gene activation can cause cancer in humans. Here we show that Neuropilin 1 (Nrp1) and Nrp2, transmembrane proteins with roles in axon guidance and vascular endothelial growth factor (VEGF) signaling, are important positive regulators of Hh signal transduction. The regulation of Hh signal transduction by Nrps is conserved between mammals and bony fish. These findings enhance our knowledge of Hh pathway regulation and provide evidence for a conserved nexus between Nrps and this important developmental signaling system.

Scientific Abstract:
The Hedgehog (Hh) pathway is essential for vertebrate embryogenesis, and excessive Hh target gene activation can cause cancer in humans. Here we show that Neuropilin 1 (Nrp1) and Nrp2, transmembrane proteins with roles in axon guidance and vascular endothelial growth factor (VEGF) signaling, are important positive regulators of Hh signal transduction. Nrps are expressed at times and locations of active Hh signal transduction during mouse development. Using cell lines lacking key Hh pathway components, we show that Nrps mediate Hh transduction between activated Smoothened (Smo) protein and the negative regulator Suppressor of Fused (SuFu). Nrp1 transcription is induced by Hh signaling, and Nrp1 overexpression increases maximal Hh target gene activation, indicating the existence of a positive feedback circuit. The regulation of Hh signal transduction by Nrps is conserved between mammals and bony fish, as we show that morpholinos targeting the Nrp zebrafish ortholog nrp1a produce a specific and highly penetrant Hh pathway loss-of-function phenotype. These findings enhance our knowledge of Hh pathway regulation and provide evidence for a conserved nexus between Nrps and this important developmental signaling system.